NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

RESEARCH ARTICLE

Arch Neuropsychiatry 2022;59:44–47
https://doi.org/10.29399/npa.25092

Neuropathic Pain and Its Relationship with Clinical Findings in Patients with Fibromyalgia

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ABSTRACT

Introduction: Fibromyalgia syndrome (FMS) is a clinical condition characterised by chronic generalised body pain, fatigue and presence of tender points. In this study, we hypothesized that FMS could be a type of neuropathic pain and investigated the relationship between neuropathic pain and sleep disturbance and depression. We also investigated the association between these clinical conditions and disease severity

Methods: Seventy-six patients who had FMS diagnosis according to 2010 ACR criteria were included in the study. Patients were evaluated by Fibromyalgia Impact Questionnaire (FIQ), Hamilton Depression Rating Scale (HAM-D), Pittsburgh Sleep Quality Index (PSQI), Douleur Neuropathique 4 Questions (DN4) and Leeds Assessment of Neuropathic Symptoms and Signs (LANSS).

Results: Patients had neuropathic pain in 92.1% of patients with LANSS and 82.9% of patients with DN4. According to the Pittsburg Sleep Quality Scale, 90.8% of patients had poor sleep quality. According to HAM-D, 82.9% of the patients had depression. The mean FIQ values of the patients were calculated as 63.16±10.73. There was a positive correlation between DN4 values and FIQ, PSQI, HAM-D and LANSS. There was a positive correlation between LANSS values and FIQ and PSQI values.

Conclusion: In this study we found the frequency of neuropathic pain high in FMS. We also found a positive association between neuropathic pain scales and depression, sleep disturbance, and fibromyalgia impact score. Pain, functionality and psychosocial characteristics should be assessed extensively to understand fibromyalgia completely. Abnormal pain process and secondary clinical conditions should be considered together.

Keywords: Depression, fibromyalgia, neuropathic pain, sleep disturbance

Cite this article as: Akaltun MS, Altındağ Ö, Akyol A, Göktürk H, Aydeniz A, Gürsoy S, et al. Neuropathic Pain and Its Relationship with Clinical Findings in Patients with Fibromyalgia. Arch Neuropsychiatry 2022;59:44–47.

INTRODUCTION

Fibromyalgia syndrome (FMS) is a clinical condition characterised by chronic generalised body pain, fatique and presence of tender points (1). Generalized pain is often accompanied by pathologies such as hyperalgesia, allodynia, sleep disturbances, cognitive dysfunctions, depression, irritable bowel syndrome, and restless legs syndrome (2, 3, 4). The prevalence of FMS is supposed to be between 2% and 8%, depending on the population analysed and the diagnostic criteria used. It is more common in females and between 40 to 60 years of age (1, 4).

Etiopathogenesis has not yet been fully elucidated, but genetic and environmental factors as well as neuroendocrine, autonomic, peripheral and central nervous system, immunological and psychological factors have been shown to be effective (5). In recent years, it has been suggested that central sensitisation mechanism may play a role in etiopathogenesis and FMS may be considered a type of neuropathic pain (6).

In this study, we hypothesized that FMS could be a type of neuropathic pain and investigated the relationship between neuropathic pain and sleep disturbance and depression. We also investigated the association between these clinical conditions and disease severity.

Highlights

- **Neuropathic pain is very common in Fibromyalgia Syndrome.**
- **Neuropathic pain in Fibromyalgia Syndrome is related to disease severity.**
- **A significant relationship was found between neuropathic pain, depression and sleep disturbance.**

METHODS

Seventy-six patients who applied to the Gaziantep University Medical Faculty Physical Medicine and Rehabilitation outpatient clinic between January 2013 and December 2013 and who had FMS diagnosis according to 2010 ACR (American College of Rheumatology) criteria were included in the study. Newly diagnosed patients who did not use drugs for FMS were included in the study. Patients who have malignant

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Received: 11.04.2020, **Accepted:** 29.06.2020, **Available Online Date:** 11.10.2020

disease, hyperthyroidism/hypothyroidism, chronic inflammatory disease, diabetes mellitus, uncontrolled heart and kidney disease, and pregnant women were not included in this study. Patients underwent detailed musculoskeletal examination by the same physician. Complete blood count, C-reactive protein, erythrocyte sedimentation rate and routine biochemical tests were studied. The Ethics Committee of Gaziantep University approved the study protocol. Patients were informed about the study and informed consents were obtained before the study.

The sociodemographic data form was used to evaluate patient information such as age, gender, and disease duration. The severity of the disease was evaluated with the Fibromyalgia Impact Questionnaire (FIQ). FIQ is an inquiry form that evaluates physical functions, working, depression, anxiety, sleeping, pain, stiffness, fatigue and well-being in patients with fibromyalgia. The maximum score is 100 and a high score indicates more severe disease (7).

Depression level was assessed by the Hamilton Depression Rating Scale (HAM-D). This scale is commonly used in studies at the onset of depressive symptoms and for follow-up evaluations. This scale, which questions depressive complaints last week, consists of 17 items and its maximum score is 53 points. The reliability and validity of the Turkish form is available (8).

Sleep disturbance was assessed by Pittsburgh Sleep Quality Index (PSQI). PSQI is a sleep questionnaire that helps to evaluate sleep quality, presence and severity of sleep disorder for the last one month period. It consists of 7 components and 19 items, and high scores indicate poor sleep quality (9).

Neuropathic pain severity was assessed by Douleur Neuropathique 4 Questions (DN4) and Leeds Assessment of Neuropathic Symptoms and Signs (LANSS). DN4, consists of four main questions, including the patient's interview (questions 1 and 2) and the patient's physical examination (questions 3 and 4). A total score of 4/10 indicates the diagnosis of neuropathic pain (10).

LANSS questionnaire contains abnormal pain-associated descriptors related to dysesthesias, thermal, paroxysmal, evoked, or autonomic symptoms. Scores higher than 12, suggest a neuropathic component in the pain perception (11).

Statistical Method

The Shapiro-Wilk test was used to analyze the compliance of the data with normal distribution. The Mann Whitney U test was used to compare non-normally distributed variables in two groups. The relationship between categorical variables was tested with chi-square test, and correlations between continuous variables were tested with Pearson correlation coefficient. SPSS 22.0 package program was used in the analyses. $p<0.05$ was considered statistically significant.

RESULTS

The study included 76 patients who were diagnosed with fibromyalgia. The mean age of the patients was 44.99±11.77 years; the duration of symptom was 6.83±6.39 years (Table 1).

Table 1. Sociodemographic data in patients with FMS

		Mean ± SD	n	%
Age (year)		44.99±11.77		
Duration of disease (year)		6.83±6.39		
BMI		28.39±5.18		
Gender	Male		5	6.6
	Female		71	93.4
Educational status	Literate + Primary school		43	56.5
	Middle school+ High school		18	23.7
	University		15	19.8
Menopause	Premenopause		40	52.6
	Postmenopause		31	40.8
Regular exercise	Yes		21	27.6
	No		55	72.4

FMS, Fibromyalgia syndrome; BMI, body mass index; SD, standard deviation.

Table 2. Clinical parameters in patients with FMS

	Mean ± SD
FIQ	63.16±10.73
HAM-D	13.17±5.93
PSQI,	9.54±3.38
LANSS	15.82±5.52
DN4	5.67±2.26

FMS, Fibromyalgia syndrome; SD, standard deviation; HAM-D, the Hamilton rating scale for depression; PSQI, Pittsburgh sleep quality index; FIQ, Fibromyalgia impact questionnaire; LANSS, Leeds assessment of neuropathic symptoms and signs; DN4, douleur neuropathique 4 questions.

The percentages of patients who had neuropathic pain according to LANSS and DN4 were found 92.1% and 82.9% respectively. According to the PSQI, 90.8% of patients had poor sleep quality. According to HAM-D, 82.9% of the patients had depression. Average FIQ score was *63.16±10.73* (Table 2).

There was a positive correlation between DN4 score and PSQI score, and HAM-D score and FIQ score (*r=0.307, p=0.007, r=0.325, p=0.004, r=0.431, p<0.0001, respectively*). There was a strong positive correlation between DN4 score and LANSS score (*r=0.655, p<0.0001*) (Table 3).

LANSS score was positively correlated with PSQI score and FIQ score, *(r=0.433, p<0.0001; r=0.348, p=0.002 respectively)*. FIQ score was positively correlated with PSQI score and HAM-D score (*r=0.303 p=0.008; r=0.281 p=0.015 respectively*) (Table 3).

Table 3. Correlations

	HAM-D	PSQI	FIQ
DN4	r=0.325, p=0.004	r=0.307, p=0.007	r=0.431, p<0.0001
LANSS	p=0.97	r=0.433, p<0.001	r=0.348, p=0.002
FIQ	r=0.281 p=0.015	r=0.303 p=0.008	

HAM-D, the Hamilton rating scale for depression; PSQI, Pittsburgh sleep quality index; FIQ, Fibromyalgia impact questionnaire; LANSS, Leeds assessment of neuropathic symptoms and signs; DN4, douleur neuropathique 4 questions.

DISCUSSION

Fibromyalgia syndrome is a chronic disease characterised by widespread pain, which is predominantly felt at deep somatic tissues, that is, in the muscles and joints. In addition to this, problems such as abnormal pain sensitivity, sleep disturbance and affective disorder are also observed in the course of the disease (12).

Neuropathic pain is a type of pain that is caused by primary damage or dysfunction of the nervous system (13). Despite the significant differences in the localisation of pain in FMS, patients' abnormal sensory perceptions and pain recognition resemble neuropathic pain. It also suggested that there may be similarities between pathophysiological mechanisms of FMS and neuropathic pain since pregabalin and antidepressants used in the treatment of neuropathic pain are also effective in FMS patients. Unlike classic neuropathic pain syndromes, nerve lesion has not been shown in fibromyalgia. In this sense, it has been proposed that fibromyalgia pain may be due to a dysfunction rather than a lesion in nervous system (14). We evaluated the frequency of neuropathic pain in the course of fibromyalgia in our patients. In this study, LANSS and DN4 measurements, which are used widely in the evaluation of neuropathic pain, were used and considerable high scores were detected. These results indicated that pain in FMS patients has neuropathic character.

In a study conducted in 2014, researchers determined that skin biopsies of fibromyalgia patients had lower epidermal nerve fiber density than healthy controls. It is therefore indicated that small fiber neuropathy may also contribute to the neuropathic pain clinic (15).

In another study investigating neuropathic pain clinic in patients with chronic pain due to FMS and rheumatoid arthritis, LANSS scores were higher in FMS patients and it was reported that this disease could be considered as a neuropathic pain (6). Koroschetz et al., compared the sensory symptoms of FMS and diabetic polyneuropathic patients and found that the severity of sensory symptoms was similar in both groups (16). Hyperalgesia, allodynia, the abnormal activation of pain-related brain regions can be shown as evidence of central pain mechanism abnormalities in FMS patients (17).

Common clinical manifestations for neuropathic pain syndromes include fatigue, sleep disturbance, stiffness, paraesthesia, headache, Raynaud-like symptoms, depression and anxiety (13, 18). We have determined that sleep quality is impaired in a significant proportion of our patients. Sleep disturbance is an important clinical component of fibromyalgia. It has even been suggested that sleep disturbance is the cause of the disease rather than its result. In electroencephalograms (EEG) of fibromyalgia patients, abnormal patterns during sleep were first reported by Moldofsky et al. (19). It has been reported that the amplitude of bioelectric activity increases during sleep transition and alpha waves occur in these patients. This abnormal pattern is entitled the alpha EEG non-REM anomaly. In our study, the positive correlation between sleep disturbance and pain severity also sheds light on pain-sleep deprivation-pain vicious cycle in fibromyalgia. If the disease is accepted as neuropathic pain, the negative consequences of sleep disturbance can be understood more easily.

In this study, we also investigated the relationship between neuropathic pain scales and disease severity in fibromyalgia. There was a positive correlation between disease severity and both neuropathic pain scales. This result showed that as the neuropathic pain scores increases so does the fibromyalgia impact scores.

The prevalence of major depression in patients with chronic pain is about three to four times greater than that reported in the general population (20). Psychological disorders are present in approximately 30–60% of FMS patients. The most common psychological disorder in FMS patients is depression. Our results also verified that a significant proportion of FMS patients had depressive mood. Additionally, there was a positive relationship between the severity of depression and the severity of neuropathic pain.

The frequency of fibromyalgia is increasing in the society. According to our current knowledge, its frequency in adults is around 5–6%. Therefore, the low number of patients and the lack of additional methods to diagnose neuropathic pain can be considered as limitations of our study.

Consequently, there are findings suggesting the significant role of neuropathic mechanisms in the development of fibromyalgia symptoms. Pain, functionality and psychosocial characteristics should be assessed extensively to understand fibromyalgia completely. Abnormal pain process and secondary clinical conditions should be considered together (18).

According to our current knowledge, fibromyalgia is yet to be regarded as neuropathic pain, but there is a need for extensive research that can shed light on this debate. Studies on neuropathic pain in patients with fibromyalgia may encourage detailed neurological examination and further investigations. We believe that the detection of neuropathic pain in the course of the disease may also help us in the search for novel treatment approaches.

Ethics Committee Approval: The Ethics Committee of Gaziantep University approved the study protocol.

Informed Consent: Patients were informed about the study and informed consents were obtained before the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- ÖA, AG; Design- ÖA, SG; Supervision- SG, AA; Resource- (-); Materials- (-); Data Collection and/or Processing- HG, AA; Analysis and/or Interpretation- MSA, ÖA; Literature Search- MSA, AA; Writing- MSA; Critical Reviews- AG, SG.

Conflict of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: The authors received no financial support for the research and/or authorship of this article.

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